PATENT APPLICATION

NEUROCEUTICAL FOR IMPROVING MEMORY AND COGNITIVE ABILITIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing of U.S. Provisional Patent Application Serial No. 60/249,046, entitled "Neuroceutical for Improving Memory and Cognitive Abilities," filed on November 15, 2000, and the specification thereof is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention (Technical Field):

This invention relates to health supplement compositions, specifically those utilizing antioxidants or phosphatides, and their use.

Background Art:

Note that the following discussion refers to a number of publications by author(s) and year of publication, and that due to recent publication dates certain publications are not to be considered as prior art vis-a-vis the present invention. Discussion of such publications herein is given for more complete background and is not to be construed as an admission that such publications are prior art for patentability determination purposes.

Health supplements are used by millions of Americans everyday, ranging from single ingredient vitamin supplements to multi-vitamins to prescription supplements incorporating hormone therapy and other medicinal treatments. A broad number of these health supplements are readily available to the public in over-the-counter formulations, many touting condition specific uses, such as the recent spate of "ultimate anti-aging formulations." One of these formulations contains 65 components and suggests ingestion of over 10,000 mg of the combination per day which, due to limitations of tablet size, requires

ingesting ten tablets each day. More popular brands of multivitamins contain between 26 ingredients (Theragran-M® by Mead Johnson) and 53 ingredients (Maxilife Phyto® by Twinlab). These "shotgun" approaches of incorporating all possible useful ingredients face not only serious criticisms, but also present serious potential dangers to a user. (*See*, Sardi, B. "What's Best in a Multivitamin," 2d Ed. (1998), San Dimas, CA, Sardi Publications, pp. 67-77.) For example, riboflavin (vitamin B_2) is known to be toxic in doses above 10 mg per day. Many supplement formulations exceed this limit, posing a potential health risk to the users.

Many health supplement formulations include substantial numbers of herbal compounds. Herbal compounds naturally contain numerous active chemical groups. These active chemical groups compete for overall effect. For example, lemon fruit has an acid content, but counterintuitively, has an alkaline effect within the human body. Grapefruit contains antioxidant herbal substances which can interfere with drugs such as felodipine (Plendil®) or nifedipine (Procardia®). It is intuitive that indiscriminate combinations of numerous herbs, each containing numerous key constituents, might have a subtractive overall effect. Garlic is often used in formulations for its antioxidant properties, but may have the side effect of combining with other components in the formulation to exceed safe limits of selenium (200 mcg/day), due to garlic's relatively high selenium content. Therefore, many supplements on the market incorporating herbal compounds may be more harmful than "healthful."

One promising way to incorporate important supplement components while reducing the potential for high dose toxicity is to utilize synergistic relationships among components. "Pharmacologic synergy" is a complementary, superadditive response resulting from the combination of two or more agents. For example, there are numerous examples of synergy between antioxidant vitamins. U.S. Patent No. 5,994,322 to Masuda cites a lecithin-vitamin B_{12} combination as synergistic. The oxidative synergy of vitamin E and phospholipid have been demonstrated as better than vitamin E alone. (*See*, Tesories, L., et al., "Synergistic Interactions Between Vitamin A and Vitamin E Against Lipid Peroxidation in Phosphatidylcholine Liposomes," Archives Biochemistry Biophysiology, (1996), vol. 326(1), pp. 57-63.) Vitamin A and vitamin E have more antioxidant synergy with phosphatidylcholine liposomes than the

respective single components. Other studies on synergy between numerous compounds for a focused outcome are surprisingly sparse.

On the flip side, other supplement formulations do not provide enough of certain supplements. Although many health supplements contain choline, a member of the B vitamin group, their formulations do not adequately address the needs created by phospholipid physiology. Phosphatidylcholine (either as a phosphomonoester or phosphodiester), is the serum transport form of choline. As can be seen in Fig. 1, phosphatidylcholine (monoester form) has a substitution on either R_1 or R_2, but not on both. (Choline is depicted for comparison to phosphatidylcholine.) This form of choline is a principle component of all cell membranes. It is especially important to have a sufficient amount of phosphatidylcholine to maintain intact nerve cell membranes. For example, cholinergic nerve cells in particular, when faced with a reduced level of serum phosphatidylcholine, will resort to autocannibalism of the phosphatidylcholine in their cell membranes to maintain their primary mission: producing the neurotransmitter acetylcholine. This degenerates nerve cell membranes, resulting in conditions such as Alzheimer's Disease related dementia. (*See*, Summers, W. K. Correspondence: Oral Tetrahydroaminoacridine in the Treatment of Senile Dementia, Alzheimer's Type, New England Journal of Medicine, vol. 316, p. 1605, (1987).) The choline in phosphatidylcholine is also the principle source of choline metabolized into two other forms of phosphatides: sphingolipids and plasmalogens. Both of these forms are necessary for proper function of the central nervous system.

One of the more important focuses of health supplements is the reduction of free radicals. Free radicals are associated with aging of the brain. (*See*, Halliwell, B., Gutteridge, J.M.C., "Free Radicals in Biology and Medicine" (3rd ed.), (2000) New York, Oxford University Press.) Oxidative injury to the nervous system has been documented in diseases such as AIDS-associated dementia, Alzheimer's disease, benign senile forgetfulness (pre-Alzheimer's disorder), Down's syndrome-associated dementia, Lewy body dementia, multi-infarct dementia, multiple sclerosis, Parkinson's disease-associated dementia, tardive dyskinesia, Wernicke-Korsakoff syndrome, and alcoholism-associated dementia. Indeed, oxidative injury may be the final common pathway leading to cell death. (*See*, Joaquin, A.M., et

al., "Functional Decline in Aging and Disease: A Role for Apoptosis," Journal American Geriatrics Society, (2001), vol. 49, pp. 1234-1240.) Numerous studies have shown benefit from the use of antioxidants in many of these disorders. (*See*, Halliwell, B., Gutteridge, J.M.C., "Free Radicals in Biology and Medicine" (3rd ed.), (2000), New York, Oxford University Press.)

Antioxidants are substances that protect against oxidative stress damage caused by free radicals. There are four generally recognized groups of antioxidants: plant extracts, vitamins, amino acids, and minerals. Vitamins are organic substances provided in relatively small quantities from the environment that are necessary for the maintenance of health. Precursors (e.g., carotene for vitamin A), vitamins having multiple forms (e.g., pyridoxine, pyridoxal, pyridoxamine), and essential oligopeptides are typically referred to as "vitamers," hereinafter to be understood as interchangeable with the term "vitamin."

As discussed above, prior art supplement compositions generally take a "shotgun" approach of providing supplements instead of providing specific formulations for other than a generalized "anti-aging" or "energy" formulation. However, U.S. Patent No. 6,048,846 to Cochran discloses a combination of supplement components designed to fight the causes of disease. The essential combination disclosed is use of at least one hormone with the supplement components. However, hormone administration can be dangerous given the potential downstream effects. This is the result of interaction with other hormones in feedback systems. The dosage range of hormones is often specific to timing of administration within the relevant physiological cycle. The '846 Patent formulation also does not necessarily result in an antioxidant net effect. For example, iron is used as a preferred mineral. Iron easily forms free radicals. Therefore, iron inclusion can cause a reduction in available antioxidants.

The present invention overcomes the problems associated with a "shotgun" supplement approach. The dosage ranges and use of synergistic component relationships overcome problems with potential toxicity. Additionally, as a targeted composition specific to neuroceuticals, the present invention provides appropriate dosages for treatment and reversal of the effects of neurological disorders in

addition to addressing the causes. There is a long-felt need in the art for a supplement composition that addresses ongoing neurological degeneration while avoiding toxic dosages of supplements.

SUMMARY OF THE INVENTION (DISCLOSURE OF THE INVENTION)

Surprisingly, and contrary to the teachings of the prior art, certain combinations of substances are found to give improved nervous system function with improved cognitive function and mental energy. The present invention is a supplement combination including at least one, and preferably at least two, phosphoesters and at least one antioxidant, preferably comprising at least one but not more than five antioxidant amino acids and at least one but not more than fifteen antioxidant vitamins and at least one antioxidant mineral.

The composition of the present invention exhibits synergistic antioxidant and restorative effects on the nervous system effective in treating neurodegenerative disorders where oxidative injury is believed to be contributory. These synergistic effects additionally allow use of lower doses of most of the individual components.

Add AI

DESCRIPTION OF THE PREFERRED EMBODIMENTS (BEST MODES FOR CARRYING OUT THE INVENTION)

The present invention is a supplement combination including at least one, and preferably at least two, phosphoesters and at least one antioxidant, preferably comprising at least one but not more than five antioxidant amino acids and at least one but not more than fifteen antioxidant vitamins and at least one antioxidant mineral. These certain combinations of substances are found to give improved nervous system function with improved cognitive function and mental energy.

The composition of the present invention exhibits synergistic antioxidant and restorative effects on the nervous system effective in treating neurodegenerative disorders where oxidative injury is believed to be contributory. These synergistic effects allow use of lower doses of most of the individual components. The specific dosing limits of the present invention avoid toxic effects from elevated levels

of components such as vitamin B_2 and selenium. Use of easily absorbed vitamin forms such as riboflavin 5' phosphate (activated vitamin B_2) or methylcobalamin (vitamin B_{12}) in the present invention also allows consistent absorption and utilization by mammals.

The composition of the present invention comprises a phosphoester. The essential phosphoester preferably comprises phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and/or phosphatidylinositol. These compounds enhance cholinergic neurotransmission and general nerve cell membrane maintenance. The dosage of phosphatidylcholine of the present invention is preferably higher than dosages generally accepted in prior art compounds for lecithin. Combinations of phosphomonoester and/or phosphodiester compounds with enhancement compounds such as DMAE (dimethylaminoethanol), L-glutamine (a precursor of GABA, an antidepressant neurotransmitter), and succinate (Krebs cycle generation intracellular energy substrate), result in unanticipated cognitive improvement.

The composition of the present invention further comprises at least one antioxidant. The preferred antioxidants of the present invention comprise herbal, amino acid, mineral, and vitamin antioxidants. Useful, herbal antioxidants include, but are not limited to, beta carotene, various bioflavonoids (co-enzyme Q10, curcuma, ginkgo biloba (preferably an extract), ginseng (preferably American, Korean or Siberian), Gotu Kola, grape pip (proanthocyanidins), and quercetin). Useful amino acid antioxidants include, but are not limited to, L-arginine, L-glutathione, L-lysine, L-methionine, L-taurine, and L-carnitine. Useful mineral antioxidants include, but are not limited to, boron, selenium (e.g., sodium selenite and selenium methionine), manganese (e.g., citrate), magnesium (preferably elemental) and zinc. Useful vitamin antioxidants include, but are not limited to, vitamins A, B, C, E and folic acid (pteroylgutamic acid). The preferred B vitamins are B_1 (thiamine HCl), B_2 (preferably riboflavin 5'-phosphate), B_3 (niacinamide), B_6 (preferably pyridoxine HCl and activated pyridoxal 5'-phosphate), and B_{12} (methylcobalamin). Other preferred vitamins are vitamin A (palminate), and vitamin E (d-alpha tocopheryl succinate). Other preferred vitamers include alpha lipoic acid, lutein, lycopene (a carotenoid),

succinate, ubiquinone (co-enzyme Q10), and zeaxanthin (a yellow carotenoid). Other forms or equivalents of these stated compounds may be utilized in alternative embodiments.

Synergy and bioavailability are unique in this formulation. For example, citrus bioflavonoids are antioxidants which also synergistically increase absorption of synthetic vitamin C, helping to maintain sustained blood levels of vitamin C in the blood. Another example of a synergistic relationship is use of acetyl-L-carnitine, which works synergistically raising sustained levels of glutathione and co-enzyme Q10. Vitamin E actually diminishes the toxicity of riboflavin. (*See*, Free Radical Biology and Medicine 1998:24, pp. 798-808.) It should be noted that not all vitamins or other components are capable of synergistic relationships. The present invention utilizes viable synergistic relationships of at least two components of the invention, preferably utilizing at least one antioxidant, to avoid toxicity, increase activity, or maintain desired component or other chemical levels. Betaine, bromelain, and papain are preferably added to help increase bowel absorption and thus bioavailability. Lutein and zeaxanthin are also preferably included, for their ability to specifically enhance the beneficial effects of beta carotene and vitamin A.

A correlate of synergy and bioavailability is avoidance of antagonistic interactions of components. For example, iron is not included in the formulation of the present invention because it forms free radicals responsible for oxidative stress damage. Therefore, use of iron in a supplement composition has a resultant reduction in the antioxidant properties of the composition.

The preferred formulation of the present invention is in Table 1.

Table 1: PREFERRED FORMULATION

COMPONENT	DAILY DOSE (2BID)	
Beta Carotene	14,000	IU
Betaine anhydrous (trimethylglycine)	250	mg
Bioflavonoids (lemon)	75	mg
Boron Citrate	79	mcg

Chromium*	200	mg
Coenzyme Q10	30	mg
Bromelain*	20	mg
DMAE (dimethyl amino ethanol)	75	mg
Folic Acid	180	mcg
Ginkgo biloba extract	60	mg
Ginseng, American (15% panax quinquefolis)	22.5	mg
Gotu kola*	80	mg
Grape pip (proanthocyanidins)	210	mg
L-Glutathione	210	mg
L-Lysine	150	mg
L-Methionine	111	mg
L-Taurine	75	mg
Lipoic acid	45	mg
Lutein *	4	mg
Manganese (citrate)	27	mg
Magnesium oxide (elemental value)	135.9	mg
Papain	15	mg
Phosphatidyl Choline	675	mg
Phosphatidyl Serine	22 5	mg
Selenium aminoate	17.4	mcg
Calcium citrate	372	mg
Succinate (Calcium base soy source)*	100	mg
Vitamin A (palmitate)	5,400	IU
Vitamin B1 (thiamine HCl	24 7	mg
Vitamin B2 (riboflavin 5'-phosphate)	9	mg
Vitamin B3 (niacinamide)	23.1	mg
Vitamin B5 (pantothenic calcium)	54	mg
Vitamin B6 (pyridoxine HCL)	23.1	mg
"Activated" Vitamin B6 (Pyridoxal 5'-phosphate)	7 8	mg
Vitamin B12 (methylcobalamin)	720	mcg
Vitamin C (buffered ascorbic acid)	663	g
Vitamin E (d-alpha tocopheryl succinate)	331	IU
Zinc (Citrate)	49 2	mg
INACTIVE INGREDIENTS:		
Ethyl cellulose	178 2	mg
Magnesium Stearate	60	mg
Croscarmellose sodium	210	mg
Cellulose	1 4	gm
Talc	160	mg
Silicon dioxide	160	mg

The preferred dosage range for the present invention is set forth in Table 2.

Table 2: PREFERRED DOSAGE RANGE OF COMPONENTS

COMPONENT	DAILY DOSE RANGE			
Acetyl-L-carnitine	0	-	1,500	mg

	Barberry	0	-	7	mg
	Beta Carotene	0	-	50,000	IU
	Betaine anhydrous (trimethylglycine)	0	-	1,000	mg
	Bilberry proanthocyanidins	0	-	70	mg
	Bioflavonoids (garlic)	0	-	2	mg
	Bioflavonoids (lemon)	0	-	150	mg
	Bioflavonoids (lime)	0	-	150	mg
	Bioflavonoids (orange)	0	-	150	mg
	Boron Citrate	0	-	100	mcg
	Chromium	0	-	225	mcg
	Coenzyme Q10	0	-	120	mg
	Curcuma	0	-	1,000	mg
	Betaine	0	-	50	mg
	Bromelain*	0	-	80	mg
	DMAE (dimethyl amino ethanol)	0	-	500	mg
	Folic Acid	0	-	250	mcg
	Ginkgo biloba extract	0	-	250	mg
	Ginseng, American (15% panax quinquefolis)	0	-	2,000	mg
	Ginseng, Siberian	0	-	400	mg
	Gotu kola*	0	-	100	mg
	Grape pip (proanthocyanidins)	0	-	1,000	mg
	L-Glutathione	0	-	2,000	mg
	L-Lysine	0	-	1,500	mg
	L-Methionine	0	-	1,500	mg
	L-Taurine	0	-	1,500	mg
	Lipoic acid	0	-	400	mg
	Lutein *	0	-	30	mg
	Lycopene	0	-	15,000	mcg
	Manganese (citrate)	0	-	50	mg
	Magnesium oxide (elemental value)	0	-	1,000	mg
	N-acetyl-L-cystine	0	-	1,500	mg
	Papain	0	-	50	mg
	Phosphatidyl Ethanolamine	0	-	500	mg
	Phosphatidyl Choline	0	-	16	gm
	Phosphatidyl Inositol	0	-	10,000	mg
	Phosphatidyl Serine	0	-	300	mg
	Quercetin (red apple)	0	-	1,000	mg
	Quercetin (red onion)	0	-	1,000	mg
	Selenium aminoate	0	-	200	mcg
	Calcium citrate	0	-	2,400	mg
	S-adenosylmethionine	0	-	800	mg
	Succinate (Calcium base soy source)*	0	-	300	mg
	Ubiquinone	0	-	600	mg
	Vitamin A (palmitate)	0	-	10,400	IU
	Vitamin B1 (thiamine HCl)	0	-	1,000	mg
	Vitamin B2 (riboflavin 5'-phosphate)	0	-	10	mg
	Vitamin B3 (niacinamide)	0	-	1,000	mg
	Vitamin B5 (pantothenic calcium)	0	-	500	mg
	Vitamin B6 (pyridoxine HCL)	0	-	500	mg
	"Activated" Vitamin B6 (Pyridoxal 5'-phosphate)	0	-	500	mg

Vitamin B12 (methylcobalamin)	0	-	1,000	mcg
Vitamin C (buffered ascorbic acid)	0	-	3,000	mg
Vitamin E (d-alpha tocopheryl succinate)	0	-	800	IU
Zeaxanthin	0	-	500	mg
Zinc (Citrate)	0	-	100	mg

The most preferred dosage range for the present invention is set forth in Table 3.

Table 3: MOST PREFERRED DOSAGE RANGE OF COMPONENTS

COMPONENT	DAILY DOSE RANGE			
Acetyl-L-carnitine	50	-	1000	mg
Barberry	1	-	5	mg
Beta Carotene	13,000	-	15,000	IU
Betaine anhydrous (trimethylglycine)	5	-	50	mg
Bilberry proanthocyanidins	20	-	50	mg
Bioflavonoids (garlic)	0.1	-	1	mg
Bioflavonoids (lemon)	50	-	100	mg
Bioflavonoids (lime)	50	-	100	mg
Bioflavonoids (orange)	50	-	100	mg
Boron Citrate	50	-	100	mcg
Chromium	175	-	225	mcg
Coenzyme Q10	25	-	50	mg
Curcuma	400	-	600	mg
Betaine	10	-	45	mg
Bromelain*	5	-	50	mg
DMAE (dimethyl amino ethanol)	150	-	250	mg
Folic Acid	150	-	200	mcg
Ginkgo biloba extract	25	-	100	mg
Ginseng, American (15% panax quinquefolis)	5	-	100	mg
Ginseng, Siberian	100	-	400	mg
Gotu kola*	50	-	100	mg
Grape pip (proanthocyanidins)	175	-	250	mg
L-Glutathione	175	-	250	mg
L-Lysine	100	-	200	mg
L-Methionine	75	-	150	mg
L-Taurine	50	-	100	mg
Lipoic acid	5	-	100	mg
Lutein *	5	-	100	mg
Lycopene	5,000	-	15,000	mcg
Manganese (citrate)	1	-	10	mg
Magnesium oxide (elemental value)	100	-	200	mg
N-acetyl-L-cystine	500	-	1000	mg
Papain	5	-	75	mg
Phosphatidyl Ethanolamine	100	-	350	mg
Phosphatidyl Choline	500	-	1000	mg
Phosphatidyl Inositol	500	-	1000	mg
Phosphatidyl Serine	5	-	100	mg

	Quercetin (red apple)	100	-	500	mg
	Quercetin (red onion)	100	-	500	mg
	Selenium aminoate	5	-	75	mcg
	Calcium citrate	200	-	500	mg
	S-adenosylmethionine	300	-	500	mg
	Succinate (Calcium base soy source)*	50	-	150	mg
	Ubiquinone	300	-	500	mg
	Vitamin A (palmitate)	2500	-	7500	IU
	Vitamin B1 (thiamine HCl)	5	-	75	mg
	Vitamin B2 (riboflavin 5'-phosphate)	5	-	9	mg
	Vitamin B3 (niacinamide)	5	-	1000	mg
	Vitamin B5 (pantothenic calcium)	5	-	100	mg
	Vitamin B6 (pyridoxine HCL)	5	-	75	mg
	"Activated" Vitamin B6 (Pyridoxal 5'-phosphate)	5	-	75	mg
	Vitamin B12 (methylcobalamin)	500	-	1000	mcg
	Vitamin C (buffered ascorbic acid)	250	-	750	mg
	Vitamin E (d-alpha tocopheryl succinate)	250	-	750	IU
	Zeaxanthin	250	-	500	mg
	Zinc (Citrate)	5	-	100	mg

These dosages avoid toxic effect, and the combinations act synergistically to allow lower dosing as well as to avoid antagonist interaction. Finally, the components utilized focus on reducing or eliminating neurodegenerative effects, and further, improving cognitive and memory abilities.

Although the formulation of the invention requires at least one phosphoester and at least one oxidant, any of the other components shown in the Tables may be added to the formulation, separately or in combination, preferably in the dosage ranges shown in the Tables.

Of these components, the preferred key components useful in the formulation are as follows: phosphoesters, DMAE, L-glutamine, succinate, beta carotene, bioflavonoids, L-carnitine, boron, manganese, magnesium, zinc, vitamins A, B, C, E, folic acid, and lutein.

The most preferred key components useful in the formulation are as follows: phophatidylcholine, DMAE, succinate, beta carotene, citrus bioflavinoids, and vitamin C.

Although the invention has been described in detail with particular reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of the

present invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all references, applications, patents, and publications cited above are hereby incorporated by reference.